310* NAS/IOM merits of conserving smallpox/variola
10/98

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To: IOMrevu@nas.edu
To: swartz.morton@mgh.harvard.edu
Fcc: NAS
Subject: My review of "Assessment ... live Variola Virus"

I am glad to have this opportunity to comment. I am familiar with the NAS/IOM review process, and have read the guidelines. Hence my responses are properly informed even if I don't spell out the details. In fact my task is very easy, the report is excellent by all the criteria, and I have but a few and limited remarks.

1. The most important is left out, though it takes a trace of humility I have found difficult to instill in other policy rviews. That is that we are probably unable to predict what would be the most important developments that could guide our needs and opportunities relative to variola. These could be in the military/political sphere (and these are mentioned), or in the scientific and technical. They might have to do with unforeseeable technical opportunities, experimental tools, model systems, chemotherapeutic agents, variant diseases: experiments we would lack either the need or the wit to design today. So that is open-ended. Successful eradication of variola stocks would be irrevocable.

That we will have a different perspective on viral pathogenesis, evolution, and management of disease 10-15 years hence is a certainty. Just what that will be is not.

2. Perhaps connected with 1., there is an underlying assumption that variola (having once evolved from who knows what) is never going to evolve again. There is some tacit recognition of unexplored variation in existing stocks.

3. One trajectory that I perhaps should have introduced into discussion myself at an earlier date: as far as I am aware we know little about recombination between orthopoxviruses. What bearing might this have on the co-circulation of vaccinia and monkeypox in immunocompromised human hosts? in monkeys? Will new, moderately human-adapted viruses emerge looking for detailed sero-matching against variola? *** v.i. for some discussion

---- Setting these strategic issues aside -----

4. p. 42 Post-exposure vaccination. Those assertions are made categorically; you may want to qualify them by the rigor of the evidence actually available.

5. p. 18 ff. The discussion of immune response, and B/T cell interconnections is vague and weak compared to rest of presentation.

None of these considerations is remotely close to being a show-stopper. The Committee has done a great job.

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*** appendix

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Title
Naturally occurring orthopoxviruses: potential for recombination with vaccine vectors.
Source
Journal of Clinical Microbiology. 36(9):2542-7, 1998 Sep.
Abstract
Orthopoxviruses are being increasingly used as live recombinant vectors for vaccination against numerous infectious diseases in humans, domestic animals, and wildlife. For risk assessments and surveillance, information about the occurrence, distribution and ecology of orthopoxviruses in western Europe is important but has mainly been based on serological investigations. We have examined kidneys, lungs, spleens, and livers of Norwegian small rodents and common shrews (Sorex araneus) for the presence of orthopoxvirus DNA sequences by PCR with primers complementary to the viral thymidine kinase (TK) gene. PCR amplicons were verified as orthopoxvirus specific by hybridization with a vaccinia virus TK-specific

probe. A total of 347 animals (1,388 organs) from eight locations in different parts of Norway, collected at different times of the year during 1993 to 1995, were examined. Fifty-two animals (15%) from five locations, up to 1,600 km apart, carried orthopoxvirus DNA in one or more of their organs, most frequently in the lungs. These included 9 of 68 (13%) bank voles (Clethrionomys glareolus), 4 of 13 (31%) gray-sided voles (Clethrionomys rufocanus), 3 of 11 (27%) northern red-backed voles (Clethrionomys rutilus), 16 of 76 (21%) wood mice (Apodemus sylvaticus), and 20 of 157 (13%) common shrews. The previous isolation of cowpox virus from two clinical cases of infection (human and feline) at two of the locations investigated suggests that the viruses detected are cowpox and that some of the virus-carrying small mammalian species should be included among the cowpox virus natural reservoir hosts in Scandinavia and western Europe.

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Title
Two types of deletions in orthopoxvirus genomes.
Source
Virus Genes. 9(3):231-45, 1995 Feb.
Abstract
The genome nucleotide sequences of two strains of variola major virus and one strain of vaccinia virus were compared. One hundred and sixty-eight short (less than 100 bp in length) and eight long (more than 900 bp in length) deletions, four deletion/insertion regions, and four regions of multiple mutational differences between variola and vaccinia virus DNAs were revealed. Short deletions generally occur at directly repeated sequences of 3-21 bp. Long deletions showed no evidence of repeated sequences at their points of junction. We suggest the presence of a consensus sequence characteristic of these junctions and propose that there is a virus-encoded enzyme that produces this nonhomologous recombination/deletion in the cytoplasm of the infected cell.